(54) Title: POLYHYDROXYALKANOATE MEDICAL TEXTILES AND FIBERS

(57) Abstract: Absorbable polyester fibers, braids, and surgical meshes with prolonged strength retention have been developed. These devices are preferably derived from biocompatible copolymers or homopolymers of 4-hydroxybutyrate. These devices provide a wider range of in vivo strength retention properties than are currently available, and could offer additional benefits such as anti-adhesion properties, reduced risks of infection or other post-operative problems resulting from absorption and eventual elimination of the device, and competitive cost. The devices may also be particularly suitable for use in pediatric populations where their absorption should not hinder growth, and provide in all patient populations wound healing with long-term mechanical stability. The devices may additionally be combined with autologous, allogenic and/or xenogenic tissues to provide implants with improved mechanical, biological and handling properties.

POLYHYDROXYALKANOATE MEDICAL TEXTILES AND FIBERS

Background of the Invention

The present invention generally relates to textile and fiber-based

5   medical devices derived from poly-4-hydroxybutyrate and its copolymers.

Poly-4-hydroxybutyrate (available from Tepha, Inc., Cambridge, MA

as PHA4400) is a strong pliable thermoplastic that is produced by a

fermentation process (see U.S. Patent No. 6,548,569 to Williams *et al.*).

Despite its biosynthetic route, the structure of the polyester is relatively

10   simple (Figure 1). The polymer belongs to a larger class of materials called

polyhydroxyalkanoates (PHAs) that are produced by numerous

microorganims, Steinbüchel, A. Polyhydroxyalkanoic acids, *Biomaterials*,

123-213 (1991); Steinbüchel A., et al. Diversity of Bacterial

Polyhydroxyalkanoic Acids, *FEMS Microbial. Lett.* 128:219-228 (1995); and

15   Doi, Y. *Microbial Polyesters* (1990). In nature these polyesters are produced

as storage granules inside cells, and serve to regulate energy metabolism.

They are also of commercial interest because of their thermoplastic

properties, and relative ease of production. Several biosynthetic routes are

currently known to produce poly-4-hydroxybutyrate, as shown in Figure 2.

20   Chemical synthesis of poly-4-hydroxybutyrate has been attempted, but it has

been impossible to produce the polymer with a sufficiently high molecular

weight necessary for most applications, Hori, Y., et al. Chemical Synthesis

of High Molecular Weight poly(3-hydroxybutyrate-*co*-4-hydroxybutyrate,

Polymer 36:4703-4705 (1995).

25   Tepha, Inc. (Cambridge, MA) produces PHA4400 and related

copolymers for medical use, and has filed a Device Master Files with the

United States Food and Drug Administration (FDA) for PHA4400. Related

copolymers include 4-hydroxybutyrate copolymerized with 3-

hydroxybutyrate or glycolic acid (U.S.S.N. 60/379,583 to Martin & Skraly,

30   U.S. Patent No. 6,316,262 to Huisman *et al.*, and U.S. Patent No. 6,323,010

to Skraly *et al.*). Tepha has also filed a Device Master File with the United

States FDA for copolymers containing 3-hydroxybutyrate and 4-

hydroxybutyrate. Methods to control molecular weight of PHA polymers have been disclosed by U.S. Patent No. 5,811,272 to Snell *et al.*, and methods to purify PHA polymers for medical use have been disclosed by U.S Patent No. 6,245,537 to Williams *et al.* PHAs with degradation rates *in*

5   *vivo* of less than one year have been disclosed by U.S. Patent No. 6,548,569 to Williams *et al.* and PCT WO 99/32536 to Martin *et al.* The use of PHAs as tissue engineering scaffolds has also been disclosed by U.S. Patent No. 6,514,515 to Williams, and other applications of PHAs have been reviewed in Williams, S.F., et al. Applications of PHAs in Medicine and Pharmacy, in

10   Biopolymers, *Polyesters, III* Vol. 4:91-127 (2002).

      In the practice of surgery there currently exists a need for absorbable fibers and surgical meshes with improved performance. For example, there is currently a need for an absorbable monofilament fiber with a prolonged strength retention that can be used as a suture material. Such a product would

15   potentially be useful in the treatment of patients with diabetes, obesity, nutritional impairment, compromised immune systems, or other conditions such as malignancy or infection that compromise wound healing.

      There also exists a need for improved surgical meshes. For example, an absorbable hernia mesh with prolonged strength retention could have

20   many advantages over the non-absorbable synthetic meshes currently used in hernia operations (Klinge, U., et al., Functional Assessment and Tissue Response of Short- and Long-term Absorbable Surgical Meshes, *Biomaterials* 22:1415-1424 (2001). Long-term implantation of these non-absorbable meshes is not considered ideal because they can lead to

25   complications such as adhesions (fistula formation), pain, and restriction of physical capabilities (Klinge et al., 2001). If implanted into surgical sites that are contaminated or have the potential to become contaminated, 50-90% of these non-absorbable implants will need to be removed (Dayton *et al.* 1986). These implants are also not ideal for use in pediatric patients where

30   they could hinder growth (Klinge et al., 2001). To date, the use of absorbable synthetic surgical meshes in hernia repair has been found to almost invariably result in large incisional hernias that require revision

operations because of the relatively short-term strength retention of these materials (Klinge et al., 2001). However, it is thought that an absorbable hernia mesh with prolonged strength retention could solve this problem providing a mechanically stable closure, reduce the incidence of adhesions

5   and risks of infection, and be suitable for use in pediatric patients.

In addition to the need for improved meshes for hernia repair, there are also needs for improved meshes and patches for other procedures. In pericardial repair there exists a need for a surgical material that will prevent adhesions between the sternum and heart following open-heart surgery.

10   There are also similar needs to prevent adhesions in spinal and gynecology procedures that could be addressed with improved surgical meshes and patches.

Biomaterial patches derived from animal and human tissue are currently used fairly extensively in cosmetic surgery, cardiovascular surgery,

15   general surgery (including hernia repair), and in urology and gynecology procedures for the treatment of conditions that include vaginal prolapse and urinary incontinence. There is however reported to be growing concern about the use of animal and human derived biomaterials because of the risks associated with disease transmission. Synthetic absorbable meshes and

20   patches that may offer decreased risks of disease transmission are currently limited, can be inflammatory, and do not provide prolonged strength retention. Thus there currently exists a need to develop new absorbable meshes for these procedures as well. Ideally, these products should have prolonged strength retention, induce minimal inflammatory responses that

25   resolve, provide mechanically stable reinforcement or closure, offer anti-adhesion properties (where necessary), minimize the risks of disease transmission, and after absorption leave a healthy natural tissue structure.

There is thus a need to develop absorbable fibers with prolonged strength retention that could be used as suturing materials, or in surgical

30   meshes. The latter, offering longer-term mechanical stability, could also be used in other procedures such as pelvic floor reconstruction, urethral suspension (to prevent stress incontinence using the mesh as a sling),

pericardial repair, cardiovascular patching, cardiac support (as a sock that fits over the heart to provide reinforcement), organ salvage, elevation of the small bowel during radiation of the colon in colorectal cancer patients, retentive devices for bone graft or cartilage, guided tissue regeneration,

5 vascular grafting, dural substitution, nerve guide repair, as well as in procedures needing anti-adhesion membranes and tissue engineering scaffolds. Strong absorbable fibers could also find other uses, for example, in synthetic ligament and tendon devices or scaffolds. Further uses include combinations with other synthetic and natural fibers, meshes and patches.

10 For example, the absorbable fibers and devices such as meshes and tubes derived from the fibers could be combined with autologous tissue, allogenic tissue, and/or xenogenic tissues to provide reinforcement, strengthening and/or stiffening of the tissue. Such combinations could facilitate implantation of the autologous, allogenic and/or xenogenic tissues, as well as

15 provide improved mechanical and biological properties. Combination devices could be used for example in hernia repair, mastopexy / breast reconstruction, rotator cuff repair, vascular grafting / fistulae, tissue flaps, pericardial patching, tissue heart valve implants, bowel interposition, and dura patching.

20   It is therefore an object of this invention to provide absorbable fibers, surgical meshes, and medical devices with one or more of the following features: prolonged strength retention *in vivo*, anti-adhesion properties, minimal inflammatory reaction upon implantation, minimal risk for disease transmission or to potentiate infection, remodeling *in vivo* to a healthy

25 natural tissue.

It is another object of this invention to provide methods for fabricating the articles and devices with prolonged strength retention.

It is yet another object of the invention to provide absorbable multifilament fibers, and methods for fabricating these multifilaments into

30 surgical meshes.

It is still yet another object of the invention to combine the fibers and meshes with autologous, allogenic and/or xenogenic tissues to provide

improved mechanical, biological and handling properties of the autologous, allogenic and/or xenogenic tissues.

Summary of the Invention

Absorbable polyester fibers, braids, and surgical meshes with

5   prolonged strength retention have been developed. These devices are preferably derived from biocompatible copolymers or homopolymers of 4-hydroxybutyrate. These devices provide a wider range of *in vivo* strength retention properties than are currently available, and offer additional benefits such as anti-adhesion properties, reduced risks of infection or other post-

10   operative problems resulting from absorption and eventual elimination of the device, and competitive cost. The devices are also particularly suitable for use in pediatric populations where their absorption should not hinder growth, and provide in all patient populations wound healing with long-term mechanical stability. The devices may additionally be combined with

15   autologous, allogenic and/or xenogenic tissues to provide implants with improved mechanical, biological and handling properties.

Brief Description of the Drawings

Figure 1 is the chemical structure of poly-4-hydroxybutyrate (P4HB, poly-4-hydroxybutyrate).

20   Figure 2 shows some of the known biosynthetic pathways for the production of P4HB. Pathway enzymes are: 1. Succinic semialdehyde dehydrogenase, 2. 4-hydroxybutyrate dehydrogenase, 3. diol oxidoreductase, 4. aldehyde dehydrogenase, 5. Coenzyme A transferase and 6. PHA synthetase.

25   Figure 3 is a graph of strength retention data of PHA4400 fibers (*in vitro* and *in vivo*) compared with PDS control fiber (*in vivo*).

Figure 4 is a graph comparing the tensile mechanical properties of PHA4400 and commercially available monofilament sutures.

Figure 5 is a graph of the degradation of PHA4400 (P4HB) samples

30   *in vivo* compared to *in vitro* controls. The Mw for implanted (*in vivo*) and buffer control sutures (*in vitro*) is plotted versus time.

Figure 6 is a graph of the ratio of mass and length of the PHA4400

sutures (*in vitro* and *in vivo*) plotted as a function of degradation time.

Detailed Description of the Invention

Absorbable fibers and meshes with prolonged strength retention have

5   been developed.

I.   Definition

Strength retention refers to the amount of time that a material

maintains a particular mechanical property following implantation into a

human or animal. For example, if the tensile strength of an absorbable fiber

10   decreased by half over 3 months when implanted into an animal, the fiber's

strength retention at 3 months would be 50%.

Biocompatible refers to the biological response to the material or

device being appropriate for the device's intended application *in vivo*. Any

metabolites of these materials should also be biocompatible.

15   Poly-4-hydroxybutyrate means a homopolymer comprising 4-

hydroxybutyrate units. It may be referred to as P4HB, PHA4400 or

TephaFLEX™ biomaterial and is manufactured by Tepha Inc., Cambridge,

MA. Copolymers of poly-4-hydroxybutyrate mean any polymer comprising

4-hydroxybutyrate with one or more different hydroxy acid units.

20   **II.   Source of Poly-4-hydroxybutyrate and copolymers thereof**

Tepha, Inc. of Cambridge, MA produces poly-4-hydroxybutyrate and

copolymers thereof using transgenic fermentation methods.

III. Poly-4-hydroxybutyrate fibers with prolonged strength retention

Around 1984, a division of Johnson and Johnson (Ethicon) first

25   introduced a monofilament synthetic absorbable suture known as PDS™,

made from polydioxanone. This suture retains about 50% of its strength up

to 6 weeks after implantation, and is completely absorbed in the body within

6 months. Davis and Geck subsequently introduced a monofilament suture

based on a copolymer of glycolide and trimethylene carbonate that is sold

30   under the tradename of Maxon™. This suture has a similar strength

retention to PDS™. Two other monofilament sutures were introduced more

recently. Monocryl™ based on segmented copolymers of glycolide and

caprolactone, and Biosyn™ based on a terpolymer of glycolide, *p*-dioxanone, and trimethylene carbonate. Monocryl™ is reported to have a 20-30% breaking strength after 2-3 weeks, and be completely absorbed after 3-4 months. Biosyn™ has an absorption profile similar to Monocryl™.

5   Despite continued innovation in the development of absorbable synthetic monofilament sutures there is still a need for a synthetic absorbable suture with extended strength retention for patients requiring long-term wound support, for example, a monofilament suture with 50% strength retention at 3-6 months (after implantation). There are also limited options for synthetic

10   absorbable meshes with prolonged strength retention.

        U.S. Patent No. 6,548,569 to Williams *et al.* discloses that poly-4-hydroxybutyrate has a slower absorption rate *in vivo* than many materials used as absorbable sutures, and provides absorption data for unoriented poly-4-hydroxybutyrate films and porous samples. It does not, however, disclose

15   the strength retention of fibers of poly-4-hydroxybutyrate following implantation.

        It has now been discovered that oriented fibers of PHA4400 and copolymers thereof can be prepared with tensile strengths comparable to existing synthetic absorbable suture fibers (such as PDS™), but have a

20   prolonged strength retention *in vivo* of over 20-30% at 3-6 months. In comparison, a control PDS suture had little tensile strength remaining after 12-15 weeks.

        It has also been discovered that oriented poly-4-hydroxybutyrate fibers can be used to prepare surgical meshes and tubes with prolonged

25   strength retention. These fiber and textile devices may further be combined with autologous, allogenic and/or xenogenic tissues to impart improved properties to these implantable tissues. Properties that can be improved through this combination include mechanical properties such as tensile strength and modulus, for example, to reinforce the tissues to make them

30   stronger, stiffer, more durable, and easier to implant.

        Non-limiting examples are given herein to describe the methods for preparing the fibers, meshes, and composite devices with autologous,

allogenic and/or xenogenic tissues, and to illustrate the strength retention of
the fibers upon implantation.

**EXAMPLE 1: Melt extrusion of PHA4400 to produce monofilament
fibers**

5   PHA4400 (Tepha, Inc., Cambridge, MA) (Mw 575K) was ground
into small pieces using a Fritsch cutting mill (Pulversette 15, 10 mm bottom
sieve) and dried under vacuum overnight prior to melt processing.
Monofilament fibers of PHA4400 were melt extruded using an AJA (Alex
James Associates, Greer, SC) 3/4" single screw extruder (24:1 L:D, 3:1

10   compression) equipped with a Zenith type metering pump (0.16 cc/rev) and a
die with a single hole spinnerette (0.026", 2:1 L:D). The 4 heating zones of
the extruder were set at 140°, 190°, 200° and 205°C. The extruder was set
up with a 15 ft drop zone, 48" air quench zone (10°C), a guide roll, three
winders and a pickup. The fiber was oriented in-line with extrusion by

15   drawing it in a multi-stage process to provide fiber with high tensile strength
and a reduced extension to break. The fiber was drawn in-line to stretch
ratios of 6 to 11X. A spin finish (Goulston, Lurol PT-6A) was dissolved in
iso-propanol at 10 vol/vol% and applied to the fiber before the first roll to act
as a lubricant and protect the fiber during downstream processing. A series

20   of fibers of different sizes were produced by varying the extrusion conditions
(metering pump speed) and drawing conditions (draw ratio). Tensile
mechanical properties of the melt extruded fibers were determined using a
universal mechanical tester, and results are shown in Table 1. As is evident,
the tensile strength of the oriented PHA4400 fiber is comparable to 450-560

25   MPa reported for the commercial suture fiber, PDS™, Chu, C.C., et al.
Wound Closure Biomaterials and Devices, CRC Press (1997). The weight
average molecular weight (Mw) of the fibers was determined by gel
permeation chromatography (GPC) and is also shown in Table 1.

Table 1. Properties of melt extruded PHA4400 monofilament.

Sample	Draw Ratio	Diameter (μm)	Load at break (g)	Tensile Strength (MPa)	Elongation to Break (%)	Mw** (K)
1	5.95	125	533	426	107	338
2	5.95	113	274	268	126	293
3	5.95	82	68	126	34	278
4	5.95	128	389	297	134	302
5	6.00	134	426	296	118	313
6	10.75	120	569	494	32	348
7	10.75	120	446	387	29	356
10*	10.75	217	1304	346	70	395
11*	5.95	190	1291	447	135	396

*Note: Samples 10 and 11 were spun through a larger spinnerette (0.045", 2:1 L:D).
**Note Mw of starting polymer was 575 K.

5   **EXAMPLE 2: Strength retention and biocompatibility of PHA4400 monofilament fibers.**

An implantation study to determine the strength retention of PHA4400 fibers was undertaken in a rabbit model. Sample 10 (shown in Table 1) was selected for these studies because the fiber had an elongation to

10   break of 70% and tensile strength of 346 MPa (60,000 psi) that is comparable to commercial monofilament absorbable sutures. Prior to implantation the fiber was sterilized using cold ethylene oxide gas (40°C, ethylene oxide pressure of 13.7 INHGA, humidity of 1.7 INHGA, dwell time 4 hr, and aeration time 10 hr). A small amount of fiber shrinkage (2%) was

15   noted to result during the sterilization process. A commercial monofilament absorbable suture material, PDS™, was used as a control.

Under sterile conditions, the sterilized sutures were placed perpendicular to the dorsal midline of the rabbit. After making a small incision, a large hemostat was introduced through the incision into the

20   subcutaneous tissue and tunneled approximately 9 inches into the subcutis layer. The PHA4400 and control (3/0 PDS™) suture fibers were threaded individually through separate surgically created implant areas and left in place. The incisions were closed with tissue glue. A total of four test and four control samples were implanted in each rabbit. Animals were

25   maintained for periods of 1, 4, 8, 12, 16 and 26 weeks (2 rabbits per time point) and were observed daily to ensure proper healing of the implant sites.

At the end of the appropriate time points, the animals were weighed and euthanized by an injectable barbituate. Tissue sections containing the implanted sutures were excised from the animals. One test and one control sample were fixed in formalin and retained for histological analysis of the

5   tissue surrounding the suture implants. The remaining three samples from each group were cleaned of tissue, wrapped in sterile, saline soaked gauze and returned on the day of explantation for further analysis. Suture samples were further cleaned of residual tissue and dried.

In parallel with the *in vivo* degradation study, an *in vitro* degradation

10   study was conducted to generate comparative data. Sterilized PHA4400 monofilament fibers, identical with those used in the implantation study, were incubated in Dulbeco's phosphate buffered saline (pH 7.4, 37°C) containing sodium azide (0.05%) as a preservative. Six control PHA4400 sutures per time point were enclosed in sterile polyethylene sample bags and

15   removed at the same time as each of the implant samples. The *in vivo* and *in vitro* samples were processed identically.

Strength Retention

The explanted suture samples were subject to tensile testing according to the procedure of ASTM D2256-97. The results of this tensile

20   testing are shown in Figure 3. As can be seen, the PHA4400 and PDS™ control sutures had very comparable starting tensile strengths (60,000 psi). As expected, the PDS™ control sutures maintained 50% of their initial tensile strength until approximately the 6th week. In contrast, the implanted PHA4400 sutures retained approximately 30% of their tensile strength

25   through the 26th week. A comparison of the tensile mechanical properties of PHA4400 and commercially available monofilament sutures is shown in Figure 4.

Unlike the implanted suture, the PHA4400 *in vitro* control suture showed a more gradual loss of strength during the entire 26-week

30   degradation study, retaining 80% of its original strength. This result demonstrates the mechanical stability of the polymeric material to simple hydrolysis.

Molecular Weight and Mass Loss

In addition to the strength retention of the PHA4400 suture fibers, the Mw of the PHA4400 samples were analyzed by GPC. As shown in Figure 5, the Mw of the implanted and control PHA4400 sutures decreased gradually

5 during the course of the degradation study to approximately 43% of their original Mw at 26 weeks. Additionally, there does not appear to be a significant difference between the Mw of the implanted and the *in vitro* control PHA4400 sutures. This result shows that the hydrolytic stability of the implanted sample is very similar to the *in vitro* control.

10 In order to determine the mass loss of the samples over time, the mass and length of the PHA4400 sutures (*in vitro* and *in vivo*) were determined and plotted as a function of degradation time. The ratio of mass to length of the PHA4400 samples (implanted and buffer control) is plotted vs. degradation time and shown in Figure 6. The mass/length ratio was

15 determined rather than just the mass of the sample, because this ratio normalizes for samples that were cut during implantation or that break during harvest. As can be seen in this figure, the implanted sutures appear to loose mass more rapidly than the *in vitro* controls. This data shows that the implanted samples lost mass more rapidly than the *in vitro* control samples

20 and suggests that surface degradation is occurring *in vivo*.

Tissue Reaction

The tissue surrounding the implanted PHA4400 and PDS™ control sutures was analyzed for the tissue reaction to the implanted articles through the 26-week time point. Formalin fixed tissue samples (PHA4400 and

25 PDS™ control) from each test animal were sectioned and graded by a board certified veterinarian for the following: inflammation, fibrosis, hemorrhage, necrosis, degeneration, foreign debris and relative size of involved area.

Hisotopathological evaluation indicated that the finding at the PDS™ control and PHA4400 sites were similar and there were no significant

30 indications of a local toxic effect in either the control or the test sites.

EXAMPLE 3: Knitted mesh of PHA4400 monofilament fibers with prolonged strength retention.

A warp knitted mesh of PHA4400 was produced from 100 μm diameter oriented monofilament PHA4400 fiber produced as described in

5　　Example 1. A warp knit type of construction is desirable as an implant because it can be cut by the surgeon and will not readily unravel. The mesh was fabricated using fiber of 100 μm monofilament PHA4400, tensile strength 92,000 psi, and an elongation to break of 77%. Fabric construction was as follows: Mach #30 Raschel Knit 36 gauge fabric, 150 ends, 16

10　　courses, 40 stitches per inch, using 18 needles per inch. Specifications for the finished fabric were: Weight: 58 g/m^2 (1.72 oz/sq. yard), Thickness: 0.29 mm.

EXAMPLE 4: Extrusion of suture fibers of a copolymer of glycolate and 4-hydroxybutyrate (PHA4422).

15　　PHA4422 containing 5% glycolic acid comonomer (Mw 305,000 by GPC) was melt extruded into a fiber and converted to a suture as follows. The polymer was prepared by milling the bulk polymer into approximately 1 mm sized particles using a P-15 laboratory cutting mill (Fritsch, Germany) dried in a vacuum desicator. The polymer was extruded using an AJA 5/8"

20　　single screw extruder (Alex James and Associates) with a single-hole spinneret (0.040"; 2:1 L/D). The extruder had five separate temperature zones that were set to 120, 154, 155, 160 and 160°C from the inlet to the outlet, with a gear pump at the outlet. The total residence time in the extruder was estimated at 9 minutes. After extrusion there was a 10 ft drop

25　　zone through air before a quenching water bath (5°C). Following the quench bath, three winders were used to collect the fiber. A first winder was set for a speed of about 2.5 meters per minute. The bath length was about 3-4 ft and the residence time for the fiber in the bath was estimated at about 30 seconds. Crystallization of the fiber occurred before the first winder. Two additional

30　　winders (17.5 and 19.5 meters/minute) extended the fiber about 8 times (8X draw). A take up unit was used with only slight tension. Varying the polymer extrusion rate while keeping the downstream orientation and take up

rates the same produced fibers of different diameters. Initially, the extruder

was set at a gear pump rate of 7, and then successively slowed resulting in

fibers of approximately 375, 275 and 200 µm diameter, see Table 2.

Suture needles were attached to each of the different diameter fibers

5   and the sutures were packaged for sterilization. Tensile strength (straight

and knot pull) was determined for representative samples of the sutures, see

Table 2.

Table 2: Physical characterization of sutures prepared by melt extrusion of
10   PHA4422 (5% glycolic acid comonomer, Mw 300K).

Fiber diameter (µm)	Corresponding USP size approx.	Tensile Strength Straight Pull (lbf)	Elongation Straight Pull (%)	Tensile Strength Knot Pull (lbf)	Elongation Knot Pull (in)
375 +/-6	0	9.2 +/-1.6	128 +/-33	4.6 +/-0.4	51 +/-4.2
256 +/-2	2/0	5.3 +/-0.3	65 +/-13	3.8 +/-0.8	49 +/-18
199 +/-5	4/0	3.0 +/-0.3	130 +/-24	1.6 +/-0.3	44 +/-15

EXAMPLE 5: Monofilament fiber with peak tensile stress of greater
15   **that 70 kg/mm^2.**

Melt spinning of Poly-4-hydroxybutyrate "PHA4400" polymer has

been extremely difficult to accomplish due to melt flow instability and

tackiness of resulting fiber. Melt leaving the spinning die exhibited periodic

diameter fluctuation and helical structure. These flow irregularities are

20   known as melt fracture or "elastic turbulence" and are generated while the

melt is entering and passing through spinneret hole. The reason for such

flow irregularities is very high viscosity of the viscoelastic melt and a very

high elastic function at the exiting point of spinneret capillary.

The low glass transition temperature of about -50 °C, and the low

25   tendency to crystallize of this polymer explain the stickiness of the fibers. In

addition to that, the orientation, which was generated during melt spinning,

relaxed after a very short time so that the fibers offered a low tenacity for

further drawing.

This example illustrates our ability to overcome the above processing problems and produce high strength fiber. PHA4400 polymer was dried to less than 0.01% moisture. Dried pellets of the PHA4400 were fed to an extruder barrel under a blanket of nitrogen. Barrel temperatures zones were

5   kept at 100°C feed, 150°C transition and 200°C metering. Molten polymer passed through a heated block to a metering pump then extruded from a die with a single hole spinneret. The block, metering pump and the die were kept at 220°C temperature. Pump discharge pressure was kept below 1000 psi by control of temperatures, and the speed of the metering pump. Spun extrudate

10 filament was free from all melt irregularities..The extrudate was allowed dwell time to crystallize after which further multi stage drawing was possible to increase crystal orientation and gain strength. The fiber was then heat treated and rolled on a winding spool. Properties of the ensuing fiber are shown in Table 3.

15

Table 3: Physical characterization of fibers prepared by melt spinning of PHA4400

Fiber Min Diam. microns	Fiber Max Diam. microns	Peak Load kgf	Min Break Strength kgf/mm^2	Min Break Strength PSI	Min Break Strength MPa
0.070	0.089	0.46	73.98	1.05E+05	726
0.129	0.178	1.80	72.37	1.03E+05	710
0.256	0.305	5.50	75.32	1.07E+05	739
0.421	0.470	13.00	74.97	1.07E+05	735
0.523	0.622	22.70	74.74	1.06E+05	733

"Diam" means Diameter

20 **EXAMPLE 6: Monofilament fibers with prolonged *in vivo* strength retention.**

The PHA4400 monofilaments prepared as in Example 5 were sterilized using cold ethylene oxide gas (40°C, ethylene oxide pressure of 13.7 INHGA, humidity of 1.7 INHGA, dwell time 4 hr, and aeration time 10

25 hr).

Under sterile conditions, the sterilized monofilament fibers were placed perpendicular to the dorsal midline of the rabbit. After making a

small incision, a large hemostat was introduced through the incision into the subcutaneous tissue and tunneled approximately 9 inches into the subcutis layer. The PHA4400 fibers were threaded individually through separate surgically created implant areas and left in place. A total of four test and

5　four control samples were implanted in each rabbit. Animals were maintained for a period of 2 weeks (2 rabbits) and were observed daily to ensure proper healing of the implant sites. At the end of the appropriate time points, the animals were weighed and euthanized. Tissue sections containing the implanted sutures were excised from the animals. Samples were cleaned

10　of tissue, wrapped in sterile, saline soaked gauze and returned on the day of explantation for further analysis. Suture samples were further cleaned of residual tissue and dried. Tensile strength was determined on a universal testing machine. The tensile breaking load of the explanted fiber after 2 weeks implantation was found to be 8.5 lbf peak load, which is 87% of that

15　of the starting fiber (9.8 lbf). Thus these fibers demonstrated a higher strength retention *in vivo* (87% at 2 weeks) when compared to the fibers in Example 2, Figure 3 (50% at 2 weeks).

EXAMPLE 7: Multifilament yarn.

20　　　　Fiber spinning was carried out in the same manner as example 5 except with the die having a multi hole spinneret (20 holes x 0.0065 inches). Extrudate yarn was allowed time to crystallize, and a super cooled stream of gaseous media / liquid mist perpendicular to the fiber axis was introduced. A subzero bath was also used and proved a suitable substitute for the gaseous

25　media. The resulting filaments were further processed through cold and heated godets, and the filaments could be oriented and heat set. Yarn tenacity of greater than 3.5 gpd (gram per denier) with 30% elongation was obtained. Representative data for the multifilament yarns is shown in Table 4.

Table 4. Tensile properties for PHA4400 multifilament yarns.

Sample	Denier per filament	Peak Load Kg	Strain at break (%)	Tenacity g/denier
1	33.8	2.43	97	3.6
2	27.1	1.69	114	3.1
3	23.7	1.92	58	4.1
4	16.2	1.12	113	3.4
5	12.8	0.99	107	3.9
6	10.3	0.71	74	3.5

EXAMPLE 8: Knitted fabric from a multifilament yarn.

5   A multifilament yarn was knitted into a tube using a single feed, circular weft knitting machine (Lamb Knitting Co., model ST3A/ZA). The width of the flat tube was approximately 9 mm. The yarn knitted very well without evidence of fiber breakage even without the addition of a spin finish as a lubricant. After cleaning and sterilization, the knitted tube appears well

10   suited for use as an absorbable medical fabric.

EXAMPLE 9: Absorbable polymeric support structure for biological tissue implant.

        PHA4400 fiber woven, knitted or braided into semi rigid support

15   tubes or PHA4400 polymer directly extruded into support tubes can be prepared with an inner diameter closely matching that of a biological substrate implant (e.g. autologous, allogenic and/or xenogenic tissue). The biological implant can be inserted into the support tube, and may optionally be secured in place, for example, by suturing, prior to implantation. The

20   addition of the support tube provides improved strength, modulus, and can make implantation easier. Similarly sheets of extruded film, woven, non-woven or knitted fabric may be rolled over a biological tissue implant and the fabric ends may be tied, sutured or glued to maintain a semi-rigid construct over the biological implant.

A woven tube was produced from 0.300 mm diameter monofilament
PHA4400 fiber extruded as described in Example 5. Using circular weaving
equipment a 10 mm inside diameter tube was produced. The tube
construction allowed insertion of an implant biological substrate and

5 provided enough stiffness to position and suture an otherwise flaccid
biological implant.

We claim:

1. A fiber comprising poly-4-hydroxybutyrate polymer wherein the fiber has a tensile strength of greater than 126 MPa.

2. The fiber of claim 1 wherein the weight average molecular weight of the fiber decreases less than 80% after implantation for 6 months.

3. The fiber of claim 1 wherein the weight average molecular weight of the fiber decreases less than 75% after implantation for 2 weeks.

4. The fiber of claim 1 wherein the tensile strength of the fiber decreases less than 80% after implantation for 6 months.

5. The fiber of claim 1 wherein the tensile strength of the fiber decreases less than 75% after implantation for 2 weeks.

6. The fiber of claim 1 wherein the elongation to break is over 20%.

7. The fiber of claim 1 wherein the polymer is a copolymer containing 4-hydroxybutyrate and one or more co-monomers.

8. The fiber of claim 7 wherein the co-monomer is glycolate.

9. The fiber of claim 7 wherein the co-monomer is 3-hydroxybutyrate.

10. The fiber of claim 1 wherein the fiber is a monofilament, multifilament, or braided structure.

11. The fiber of claim 1 wherein the fibers of the polymer have been oriented.

12. A device comprising one or more of the fibers of claims 1-11 wherein the device is a medical textile, tube, general surgical mesh, hernia mesh, pericardial patch, anti-adhesion patch, cardiovascular patch, guided tissue regeneration patch, sling, monofilament suture, multifilament suture, braid, ligament, tendon, meniscus repair device, cartilage repair device, nerve guide, stent, vascular graft, and dura.

13. The device of claim 12 wherein the device is a knitted mesh, woven mesh, or nonwoven mesh.

14. The device of claim 12 wherein the weight average molecular weight of the fiber in the device decreases less than 80% after implantation for 6 months.

15. The device of claim 12 wherein the weight average molecular weight of the fiber in the device decreases less than 75% after implantation for 2 weeks.

16. The device of claim 12 wherein the tensile strength of the fiber in the device decreases less than 80% after implantation for 6 months.

17. The device of claim 12 wherein the tensile strength of the fiber in the device decreases less than 50% after implantation for 2 weeks.

18. The device of claim 12 wherein the breaking strength of the device is at least 10 psi.

19. A method of use of the device of claim 12 comprising inserting into a patient in need thereof in pelvic floor reconstruction, urethral suspension to prevent stress incontinence, hernia repair, pericardial repair, cardiovascular patching, cardiac support, myocardial regeneration, organ salvage, elevation of the small bowel during radiation of the colon in colorectal cancer patients, bone, cartilage, and meniscus grafting procedures, guided tissue regeneration, vascular grafting, dural substitution, nerve repair, prevention of adhesions, ligament and tendon repair, mastopexy/breast reconstruction, vascular grafts / fistulae, GI resection (including TEF repair), tracheal reconstruction, intracardiac defect closure, support in disc herniation palliation, urinary bladder repair, and encephalocele / meningomyelocele repair.

20. A device that is formed by combining the device of claim 12 and/or the fiber of any of claims 1-11 with harvested autologous tissue, allogenic tissue, and/or xenogenic tissue.

21. The device of claim 20 wherein the devices of claim 11 and/or fiber of claims 1-10 reinforce, support, strengthen, and/or stiffen the autologous, allogenic, and/or xenogenic tissues.

22. The device of claim 20 wherein the devices of claim 11 and/or fiber of claims 1-10 stiffen the tissue to facilitate implantation.

23. The device of claim 20 wherein the harvested autologous tissue, allogenic tissue, and/or xenogenic tissues include vascular grafts, heart valves, pericardium, skin, intestine (including small intestine submucosa),

muscle, ligament and tendon, cartilage and meniscus, nerves, dura, fascia, and organs.

24. The use of the device of claim 20 in hernia repair, mastopexy / breast reconstruction, rotator cuff repair, vascular grafting / fistulae, tissue flaps, pericardial patching in intracardiac repair, tissue heart valve implants, bowel interposition, and dura patching.

25. A method for producing the fibers of claims 1-11 wherein the fiber is spun and drawn in-line to yield a fiber with a tensile strength greater than 126 MPa.

26. A method for producing a multifilament yarn of claims 1-11 wherein the yarn is spun and drawn to yield a yarn with a tenacity of greater than 0.5 g/denier.

27. The method of claim 26 wherein the yarn has a tenacity greater than 1 g/denier.

28. The method of claim 26 wherein the yarn has a tenacity greater than 3 g/denier.

29. The method of claim 26 wherein the yarn has a tensile strength of greater than 126 MPa.

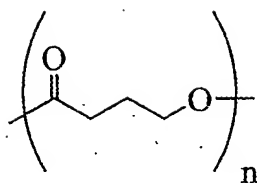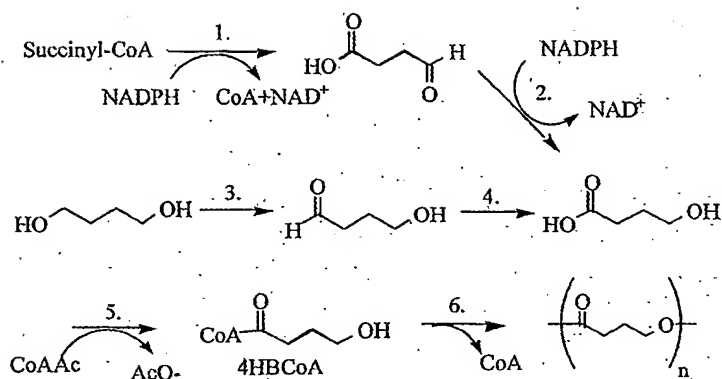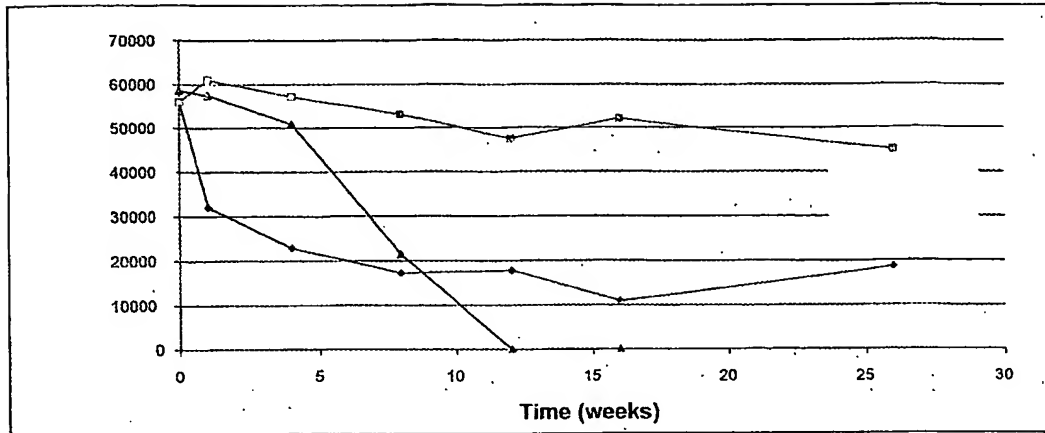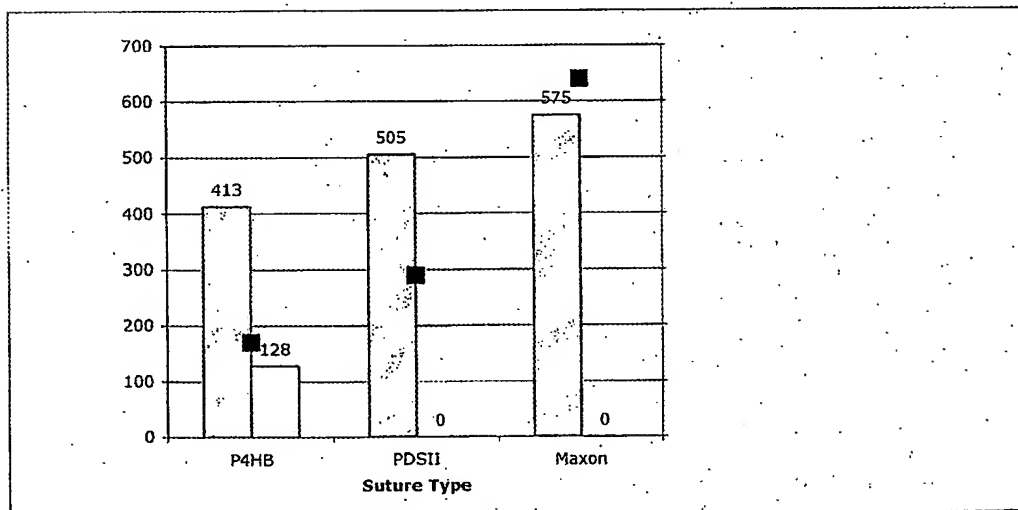30. The method of claim 26 further comprising making a medical textile from the yarn.

FIGURE 1

FIGURE 2

FIGURE 3

FIGURE 4

FIGURE 5

FIGURE 6